LARA Quarterly Progress Report: 10/1/22 – 1/15/23

Wayne State Warriors Marijuana Clinical Research Program:
Cannabinoid Adjunct to Prolonged Exposure & Recovery (CAPER)

Leslie H. Lundahl, PhD, Co-Principal Investigator
Christine Rabinak, PhD, Co-Principal Investigator

Project Aims:

In this randomized, double-blind, placebo-controlled clinical trial we will recruit veterans with PTSD who report limited prior use of cannabis along with interest in trying cannabis as a therapy. A total of 350 veterans will be randomized into one of five different THC (Δ^9-tetrahydrocannabinol:CBD (cannabidiol) dose conditions (High THC:High CBD; High THC: Low CBD; Low THC:High CBD, Low THC:Low CBD, and placebo). All participants will undergo a standardized 10-session prolonged exposure (PE) treatment protocol, consisting of two introductory/preparation sessions followed by eight exposure sessions. One to two sessions will occur each week. Just prior to beginning actual exposure sessions 1-4, participants will receive their assigned THC:CBD (or placebo) dose. We will assess treatment response (e.g., reduced PTSD symptom severity and suicidal ideation) at each subsequent PE visit, to detect rate of improvement, and again at 3-, 6-, and 9-months following treatment to explore long-term effects of PE coupled with THC:CBD vs. placebo. **Primary outcomes** include treatment response (i.e., clinical assessments of PTSD symptom severity, mood and anxiety symptoms, suicidality, and disability). **Secondary measures** include: (1) neurocognitive and reward decision-making functions (which could moderate the effects of cannabis and PE on treatment outcomes); (2) overall health, sleep quality, pain, healthcare utilization, and quality of life; (3) individual differences in fear reactivity, which has been associated with PTSD symptom severity; (4) saliva for DNA analysis to examine genetic and epigenetic markers associated with the endocannabinoid (eCB) system; and (5) blood, urine, and saliva samples to quantify levels of eCBs and their metabolites (e.g., anandamide [AEA] and 2-AG), as well as THC and CBD and their metabolites, to examine whether these levels vary as a function of THC:CBD dose mixtures and differentially affect outcomes. Data will be analyzed to determine which THC and CBD levels might be associated with the outcome measures. These data will be used to: (1) develop a predictive algorithm that will help determine personalized profiles of patients who may be at increased risk for suicide; and, (2) develop a profile of who might most benefit from cannabinoid therapeutics in combination with evidence-based behavioral treatment.

1. Project Milestones – Percent (%) completion of the project objectives

N/A. We are currently in the start-up process and the study has not yet begun.

2. Project Progress – Brief outline of the work accomplished during the reporting period and the work to be completed during the subsequent reporting period(s).

2.1. Current Progress

For this first quarter Co-PIs Lundahl and Rabinak have had several meetings (at least biweekly) with the Co-I's and research staff (in person and via electronic communication) to discuss study initiation. In addition, to support an increase in research staff necessary to carry out this trial and the large number of study participants Co-PIs Lundahl and Rabinak's research space will be expanded. Specifically, Dr. Rabinak's research lab has added an additional screening and therapy room, an additional blood draw station, and additional office space for up to 4 additional staff. The furniture for the screening/therapy room and blood draw station have been ordered and

are expected to arrive in 10-12 weeks. The additional office space for staff has been set-up. Dr. Lundahl's laboratory has been allocated more than 3,600 square feet of additional space by the Department of Psychiatry and Behavioral Neurosciences and over the past several months we have begun to move into the new space. The space includes 4 new participant testing and interview rooms, a new phlebotomy and biological sample storage room, and a new physiological testing room. This expansion has also added office space for 5 new research assistants, 2 new research coordinators, 4 new Postdoctoral Fellows, 10-12 'hot desk' workstations for students and research volunteers, a new conference room, a waiting room for veterans and their caregivers, and a media room for on-site recruitment. We have also added a "Living Room," a safe and quiet, comfortable space for veterans in emotional distress. This expansion will provide more usable space for our study participants and staff, and demonstrates the commitment of support from the Department to these VMR projects.

Below are specific tasks in which we are currently engaged:

2.2. Research personnel

- Hire and train research assistants and study coordinator
    - Sarah Durack started as a research assistant in Dr. Rabinak's lab on October 17th, 2022.
    - Dr. Rabinak has interviewed (Dec. 2022) a postdoctoral candidate and he is planning to start at the beginning of summer 2023.
    - Kayleigh Yates started as a research technologist in Dr. Rabinak's lab on October 31st, 2022.
- Research staff has begun training on study procedures (study protocol, including data collection and scoring, the use of the electronic data capture system (Castor), diagnostic interviews, and establish inter-rater reliability for clinician-administered measures; train research staff on acquisition and processing of fMRI; train research staff on blood draw protocols, processing of blood samples, and collection of other biological samples)
- Dr. Rauch is scheduled to visit WSU Jan 16-17, 2023 to conduct training in prolonged exposure therapy with study staff.
- Training cases for the study clinicians have been arranged. It is expected that therapists will be fully trained within 6 months. During this time the regulatory pieces should all be finalized.

2.3. Regulatory

- The Department of Psychiatry and Behavioral Neurosciences (DPBN) requires that all research protocols involving human participants be reviewed and approved by a Departmental Review Board (DRB) prior to submission to the broader University Institutional Review Board (IRB). We are currently working on the documents required by the DRB and plan to submit our initial DRB application in late January 2023, and anticipate receiving DRB approval of our protocol in early February 2023. Simultaneously, we have begun to prepare all documents (refining eligibility criteria, exclusion criteria, screening protocol; finalizing consent form & human subjects protocol; advertisements) required for submission to and approval by the Wayne State University IRB. Once the DRB approval is received we will submit the finalized protocol to the Wayne State University IRB in early March 2023. We expect approval will take 1-2 months, depending on revisions requested.
- Registering study to clinicaltrials.gov.
- We have begun the Import/Export process to purchase cannabis from the Office of Medicinal Cannabis (OMC) in the Ministry of Health in the Netherlands. Once our request

to purchase cannabis for research is approved a contract will be drawn up between OMC and Wayne State University.
- Preparing FDA IND application and request for DEA approval of Import license for OMC.

2.4. Protocol
- We have been assembling a clinical trial regulatory binder, which is a central organized file (electronic on Dr. Rabinak's server) that houses documents pertaining to the conduct of the study (e.g., Institutional Review Board (IRB) approvals, CVs, licenses, meeting minutes, template case report forms, etc.).
- Finalizing the study protocol, including the creation of standard operating procedures for all study tasks and a centralized manual of procedures.
- Preparation of materials for patient enrollment (purchasing and preparing all diagnostic interviews, self-report questionnaires, patient/therapist workbooks, and equipment; pilot test fMRI scan sequence protocol).
- Developed electronic versions of necessary questionnaires and measures in Castor.
- Developed databases for securely storing participant information using Castor.
- Refining timeline of study methods
- We will be following the NIH guidelines and providing THC and CBD in standardized 5 mg doses.
- The protocol for collecting plasma samples and analyzing endocannabinoids has been developed.

2.5. Supplies/Equipment
- Loaded software and measures needed for task administration and data collection.
- Dr. Rabinak ordered and received a data server for the storage of data collected during the trial. Her research technologist is currently setting up the server for study staff access.
- Obtained price estimates for EKG machine, vitals monitors, phlebotomy chair, Breathalyzers, and camera installation for participant rooms. Purchase orders are being submitted for this equipment.
- Dr. Lundahl created and purchased Warrior C.A.R.E Promotional materials for recruitment events such as shirts, banners, stickers, and stress balls.
- Dr. Rabinak is working on setting up the Eugene Applebaum building as a Labcorp pickup site for blood samples.

2.6. Safety
- Arranging for medical coverage and backup during screening and study visits.
- Developing Data Safety Monitoring Plan for identifying and reporting Adverse Events, safety protocols for increased symptomatology and/or suicide risk; maintaining confidentiality; securing data, etc. We are also identifying and sending invitations to potential DSMB members.

2.7. Recruitment and Screening
- Developing scripts for telephone screening and recruitment
- Developing advertisements for online postings and flyers
- Researched social media and local recruitment sites
- Developing study information and description to add to WarriorCARE website for recruitment (pending IRB approval of study-related materials)

2.8. <u>Planned Activities during the Next Reporting Period</u>

2.8.1. Obtain DRB approval.

2.8.2. Obtain WSU IRB approval.
2.8.3. Obtain MRI approval and establish scan sequences.
2.8.4. Pursue import/export option to obtain cannabis products from overseas cannabis grower (file FDA IND application and obtain DEA approval)
2.8.5. Once the protocol is approved we will be able to begin recruiting and screening for study enrollment. We will place ads, post flyers on main campus at around the Detroit Veterans Affairs (VA) hospital, and leverage our connections with Veterans' groups and the Detroit and Ann Arbor VA to recruit potential participants.
2.8.6. Research staff will continue training (train research staff on study protocol, including data entry and scoring, diagnostic interview, and establish inter-rater reliability for clinician-administered measures; train research staff on acquisition and processing of fMRI; train research staff on blood draw protocols and processing of blood samples);
2.8.7. Dr. Rauch will visit Detroit (Jan 16-17, 2023) to provide training in prolonged exposure therapy to our research therapists.
2.8.8. We will hold a day-long study kick-off meeting during which all research staff will be trained on the study procedures and reporting of adverse events and unanticipated problems.

2.9. Noteworthy Accomplishments – Identify and describe any milestones reached or noteworthy accomplishments completed during the period.

N/A – Still in study start-up

3. Delays – Brief description of problems or delays, real or anticipated, which should be brought to the attention of the Grant Administrator.

N/A – Still in study start-up

4. Statement concerning any significant deviation from the previously agreed-upon Statement of Work.

None.

5. **Financial expenditures of grant money and other contributions to the project, in-kind and/or direct funding.**

Wayne State University: 2022 Veteran Marijuana Research Grant
Title: Wayne State Warriors Marijuana Clinical Research Program: Cannabinoid Adjunct to Prolonged Exposure & Recovery (CAPER)

CATEGORY	TOTAL BUDGET	Expenses- thru 12/31/22	% of Budget Spent
Personnel/Fringe	4,929,150	20,227	
Equipment	-	-	
Supplies/Other	2,453,886	9,198	
Computers	18,249	-	
Emory Subcontract	813,245	32,541	
Consultants	48,893	-	
Travel	16,000	-	
DIRECT TOTALS	**8,279,423**	**61,966**	**0.75%**
Indirect Costs- 10%	827,942	6,197	
BUDGET TOTALS	**9,107,365**	**68,163**	**0.75%**

6. **Attachments and Other Materials – Provide project materials developed and implemented during the reporting period (e.g. newspaper articles, newspaper advertisements, forms, brochures, announcements, studies, reports, analyses, audits, etc.)."**

As expected, this project has received local interest and some media coverage which may serve to facilitate study activities and recruitment within the community. This coverage has included interviews at the University level.

From WSU School of Medicine: "The year in review: our top stories of 2022 at the School of Medicine"

Respectfully submitted,

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